

WHAT IS CLAIMED IS:

- 5 1. A method for obtaining a mammalian cell containing a genomic deletion greater than 15 kb, which method comprises modifying the genome of said cell containing the wild-type locus by introducing a construct comprising two regions of sequences which are homologous to the 5' and 3' flanking sequences of the region to be deleted in said wild-type locus.
- 10 2. The method of claim 1 which further comprises the steps of
 a) identifying cells containing said deletion by selecting cells containing a selectable marker present in said construct; and
 b) recovering cells containing said deletion.
- 15 3. The method of claim 1 wherein said target locus is the HPRT locus.
- 20 4. The method of claim 1 wherein said target locus is the MHC Class I locus.
- 25 5. The method of claim 1 wherein said target locus is the MHC Class II locus.
6. The method of claim 1 wherein said target locus is the immunoglobulin locus.
7. The method of claim 1 wherein said mammalian cell is selected from the group consisting of the islets of Langerhans, adrenal medulla cells, osteoblasts, osteoclasts, epithelial cells, endothelial cells, B lymphocytes, T lymphocytes, neurons, glial cells, ganglion cells, retinal cells, keratinocytes embryonic stem (ES) cells, liver cells, bone marrow cells, and muscle cells.
8. A mammalian cell prepared by the method of claim 1.

9. A method for obtaining a mammalian cell with a deletion within the range of greater than 15 to approximately 3000 kb in a target locus, which method comprises modifying the genome of said cell containing the wild-type locus by introducing construct comprising two regions of sequences which are homologous to the 5' and 3' flanking sequences of said wild-type locus.

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10. The method of claim 9 which further comprises the steps of
a) identifying cells containing said deletion by selecting cells containing a selectable marker present in said construct; and

10 b) recovering cells containing said deletion.

11. A method for preparing a mammalian cell deficient in HPRT, which method comprises introducing into target cells containing a wild-type HPRT locus a construct which comprises a modified DNA fragment, said fragment corresponding to the genomic site at which the wild-type HPRT locus is located,

15 wherein said DNA fragment comprises a first sequence immediately downstream of the second exon of the hprt locus congruent with the wild-type sequence 55 kb upstream of said first sequence in the native DNA containing wild-type HPRT locus.

20 12. The method of claim 11 which further comprises the steps of

a) identifying cells containing said deletion by selecting cells containing a selectable marker present in said construct; and

b) recovering cells containing said deletion.

25 13. A mammalian cell prepared by the method of claim 11.

14. An ES cell prepared by the method of claim 11.

30 15. A mammalian cell line which comprises in its genome, a 55 kb deletion immediately upstream of the second intron of the HPRT locus.